

REMARKS

The Applicants acknowledge the Office Action, a **Final Rejection**, of August 17, 2009 with appreciation. Claims 17-32 and 34-37 remain pending in the application; however, Claims 27, 29, and 31 remain withdrawn as a result of the previously issued Restriction Requirement. The previous rejection under 35 USC § 112, second paragraph, has been withdrawn. The Office maintains a rejection under 35 USC § 103.

Claims 17-26, 28, 30, 32, and 34-37 remain rejected for obviousness under 35 USC § 103(a) based on the disclosure of Garthwaite, et al. (US Published Application No. 2002/0132001) in view of Guez, et al. (US Patent No. 6,653,336). New Claim 38 is also subject to this obviousness rejection.

The Office reiterates its position that Garthwaite, et al. teach a composition comprising dual antihypertensive agents wherein the first agent is eplerenone and the second agent is preferably a different antihypertensive agent such as a diuretic or an ACE inhibitor. It is the further position of the Office that Garthwaite, et al. disclose (in the Table at paragraph [0087]) that perindopril is an example of an ACE inhibitor, indapamide is a example of a diuretic and that eplerenone is also disclosed as an example of a diuretic. The Office states that the reference also discloses (in Claim 17) that the disclosed composition may be a capsule comprising enterically coated pellets. The Office goes on to state that the specification further discloses the preferred characteristics/components of the pellets, including characteristics/components of the core formulation (e.g., cellulose or cellulose derivatives, including lactose and microcrystalline cellulose), the coating (e.g. including enteric coatings produced from polymerized acrylates), and additional excipients (e.g., diluents, disintegrants, binding agents, and wetting agents) and that specific dosage formulations such as tablets and hard gelatin capsules are taught by Examples 1-3 and 4-7, respectively. The Office acknowledges that Garthwaite, et al. do not expressly teach microcapsules comprising the elected t-butylamine salt of

perindopril or a combination of microcapsules comprising perindopril t-butylamine and microcapsules comprising indapamide.

The Office also reiterates its position that Guez, et al. disclose orally administering a combination dosage form comprising an ACE inhibitor and a diuretic for the treatment of arteriolo-capillary microcirculatory disorders such as arterial hypertension, and that the reference further discloses that the preferred combination is perindopril t-butylamine and indapamide. The Office further states that Examples 1 and 2 teach tablet formulations comprising perindopril t-butylamine and indapamide, and that Example 19 discloses that the perindopril t-butyl amine-indapamide combination decreases arterial pressure. The Office acknowledges that Guez, et al. do not expressly teach the two preferred active ingredients (i.e., perindopril t-butyl amine and indapamide) in the form of microencapsulated pellets or granules nor does the reference expressly teach compositions wherein the two active ingredients are encapsulated separately from one another but contained in the same dosage form.

It is the position of the Office that Garthwaite, et al. teach enterically coated particles comprising a first anti-hypertensive agent, specifically a diuretic, and an additional hypertensive agent, such as an ACE inhibitor. It is the further position of the Office that one skilled in the art would have been motivated to replace the potassium-sparing diuretic of the combination composition disclosed in Garthwaite, et al. with a thiazide diuretic (such as indapamide).

The Office again cites The Drug Monitor to support its allegation that one skilled in the art would recognize that eplerenone (a potassium-sparing diuretic) and indapamide (a thiazide diuretic) are both diuretics which are useful for the same purpose. The Office reiterates its position that, despite their "chemical distinction", both of the above-mentioned substances target the renal system to increase excretion of water from the body and both substances share at least one chemical pathway by which the elevated water excretion is achieved (i.e., by preventing the reabsorption of sodium and chloride ions).

The Office also reiterates its position that Garthwaite, et al. and Guez, et al. teach overlapping technology, namely tablet and/or gelatin capsule dosage forms comprising two active agents admixed with hydrophilic and hydrophobic polymeric additives, and that Guez, et al. specifically teach that a combination of perindopril t-butylamine and indapamide is effective in alleviating arterial hypertension or pressure.

Thus, it remains the position of the Office that, in view of the combined teachings of the cited references, it would have been obvious to one skilled in the art to prepare a composition comprising hydrophilic/hydrophobic polymer encapsulated perindopril and indapamide particles to arrive at the instantly claimed invention.

With respect to the Applicants' previously submitted argumentation regarding the references of record in the instant application, the Office provides the following analysis.

With respect to the Garthwaite, et al. reference, the Office "respectfully disagrees" with the Applicants' position that this reference does not teach a composition comprising an aldosterone antagonist in combination with an ACE inhibitor, specifically, let alone compositions comprising both active ingredients in a reservoir microcapsule dosage form for the delayed-release and controlled-release of a drug active.

The Office acknowledges that Garthwaite, et al. disclose compositions which deliver aldosterone antagonists, preferably eplerenone; however, the Office goes on to state that the "preferred teachings or conditions of a particular reference do not constitute a teaching away of the prior art." The Office further states that Garthwaite, et al. expressly teach additional embodiments such as combined active compositions. The Office reiterates its position that, according to Table 1 of the Garthwaite, et al. reference, eplerenone and indapamide appear to be preferred diuretic ingredients which are functionally equivalent, and perindopril is disclosed as a preferred ACE inhibitor. The Office states that paragraph [0089] of the Garthwaite, et al. reference "expressly suggests" that the two active ingredients

selected for the combined formulation may be enterically coated, particularly since the reference teaches that the disclosed formulations have both a delayed release in addition to an extended release component. Therefore, it is the position of the Office that Garthwaite, et al. expressly suggest that the combined composition may be created wherein indapamide is selected as the diuretic and perindopril is selected as the ACE inhibitor.

With respect to the Guez, et al. disclosure, the Office states that this reference is relied on to show that the t-butylamine salt of perindopril and indapamide (i.e., "the elected actives") are a preferred combination for co-encapsulation in an oral dosage form. Thus, although (as noted above) the Office acknowledges that the Garthwaite, et al. reference does not disclose compositions comprising the "elected actives" as those which are enterically coated and encased together within the same capsule, it is the position of the Office that the teachings of the Garthwaite, et al. and Guez, et al. references would highly motivate one skilled in the art to create the individually coated microparticles since the Garthwaite, et al. reference expressly suggests the structural teachings of the individually coated actives and the reference also suggests that eplerenone and indapamide are functionally equivalent diuretics. The Office goes on to state that both Garthwaite, et al. and Guez, et al. disclose that the final dosage form may be in the form of a gelatin capsule, thereby providing a teaching of "controlled release."

With respect to the Applicants' previously submitted argumentation that the cited references neither teach nor suggest a combination of a hydrophobic/hydrophilic polymer which is effective for providing both a delayed and controlled release profile for perindopril, the Office states that, since both the components and the ranges of the instantly claimed composite material are expressly taught by the Garthwaite, et al. reference, the adjustment of percentages of the polymeric coating materials is well within "the purview of the skilled artisan to formulate."

The Applicants respectfully submit that the Office allegation that the Garthwaite, et al. reference teaches ***enterically coated particles*** comprising a first

antihypertensive agent, specifically a diuretic, and an additional anti-hypertensive agent, such as an ACE inhibitor, is without basis.

Despite the fact that the Office "respectfully disagrees" with the Applicants' analysis regarding the Garthwaite, et al. disclosure, the Applicants respectfully reiterate that the Garthwaite, et al. disclosure relates to a composition comprising a delayed-release formulation of an aldosterone antagonist drug (preferably eplerenone). This reference further discloses that the compositions comprising the delayed-release formulation of an **aldosterone antagonist drug** may also comprise a second formulation containing an antihypertensive agent. The list of examples for such antihypertensive agents includes diuretics and ACE inhibitors. The Applicants note that Claims 1, 14, and 17 as well as the passages relied on by the Office at page 8 of the Office Action to support the above-mentioned allegation that this reference teaches **enterically coated particles** comprising a first antihypertensive agent, specifically a diuretic, and an additional anti-hypertensive agent, such as an ACE inhibitor, relate to the disclosed compositions comprising a delayed-release formulation of an aldosterone antagonist drug not to compositions comprising a **combination** of an aldosterone antagonist and another antihypertensive agent. Claims 9 and 10 relate to compositions comprising combinations; however, these claims are not directed to enterically coated pellets. Moreover, there is no disclosure of such composition.

With respect to the disclosure at paragraph [0089] of the Garthwaite, et al. reference, which disclosure is alleged by the Office to "expressly suggest" that two active ingredients selected for the combined formulation may be enterically coated, the Applicants note that this passage also refers to combinations comprising an aldosterone antagonist and a second anti-hypertensive agent.

Moreover, in order to further illustrate the differences between the instantly claimed microcapsule compositions and the compositions disclosed in Garthwaite, et al., the Applicants draw the Office's attention to paragraph [0102] of the Garthwaite, et al. reference. This passage of the Garthwaite, et al. reference relates to delayed release properties of enterically coated compositions and discloses that such

compositions are preferably comprised of an ***immediate release*** core containing an aldosterone antagonist. This passage of the Garthwaite, et al. reference further discloses that an extended release core can be useful in some circumstances but is generally not preferred as it may not release sufficient drug and that the combination of delayed release provided by the enteric coating and extended release provided by the core formulation may result in a clearance time for the drug that is too long. In other words, the Garthwaite, et al. reference itself suggests that the disclosed compositions are not particularly useful for provided a delayed and controlled release of drug.

Thus, although the Garthwaite, et al. reference discloses compositions comprising aldosterone antagonists such as eplerenone in combination with other antihypertensive agents, and the reference discloses that eplerenone and indapamide are diuretics and that perindopril is an ACE inhibitor, the reference does not disclose a composition comprising ***any*** diuretic in combination with an ACE inhibitor, let alone a compositions comprising both active ingredients in the form of microcapsules, i.e., enterically coated particles, which display acceptable delayed and controlled release characteristics.

Moreover, The Drug Monitor reference relied on by the Office to demonstrate that one skilled in the art would recognize that eplerenone and indapamide are useful for the same purpose, actually discloses that members of the class of "potassium sparing" diuretics (e.g., amiloride, triamterene, and aldosterone antagonists) act through different mechanisms. The reference also discloses the different therapeutic indications and side effect profiles for the different classes of diuretics. The reference does not disclose that all diuretics are useful for the same purpose. In fact, it discloses quite the opposite, the purpose of the article being to demonstrate and explain the differences between the various treatment options. Thus, the Applicants respectfully submit that this reference actually demonstrates that diuretics (even those belonging to the same class) have different properties/characteristics and are not interchangeable.

The courts have held that the mere fact that it might be ***possible*** to select elements of an invention by combining elements of references does not make out an obviousness rejection. See In re Bergel, 130 USPQ 206, 208 (CCPA 1961). More recently, the Court of Appeals for the Federal Circuit has held that "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole." In re Kahn, 78 USPQ2d 1329 (CAFC 2006)(cited with approval by the court in the KSR decision).

Under 35 USC § 103, in order to establish a *prima facie* showing of obviousness, it must be demonstrated that "...the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which the subject matter pertains..." The Applicants respectfully submit that Garthwaite, et al. do not disclose compositions containing two active ingredients formulated as microcapsule compositions nor does this reference disclose a composition comprising a microcapsule composition containing an ACE inhibitor such as perindopril. Moreover, the Office acknowledges that Guez, et al. do not teach such compositions.

Thus, the Applicants respectfully submit that the Office has not demonstrated a motivation to combine the disclosures of the Garthwaite, et al. and Guez, et al. references and that even if such a motivation existed, the combined disclosure of the cited references would not render the instantly claimed invention obvious because the Office has not identified prior disclosure of each element of the instant claims.

With respect to the WUTHRICH Declaration submitted with the previous Response, the Office states that the Declaration has been fully considered but is not persuasive. It is the position of the Office that the data presented in the Declaration are not commensurate in scope with the claims for the following reasons:

The Office states that no data related to compositions comprising a combination of perindopril and indapamide are presented.

The Office states that, although the study clearly contrasts immediate-release versus delayed-release preparations of perindopril/perindoprilat, the study further contrasts type I versus type II delayed-release microparticles. It is the position of the Office that the study is not persuasive because there is no clear reconciliation between the two (2) types of microparticles which appear to have different release profiles.

With respect to the "latent period" of about four (4) hours and the "controlled release period" of about twelve (12) hours discussed in the Declaration, the Office states that, for both the perindopril and perindoprilat dosage forms, it appears that a measurable amount of drug is released during the "latent period." The Office states that, for the perindopril dosage form, the type I microparticles plateau in their release of drug well before the four-hour time point and that the type II microparticles also release the drug prior to the four-hour time point which marks the end of the latent period.

The Applicants respectfully submit that the Office allegation that the study presented in the Declaration **contrasts** the characteristics of formulations comprising type I microparticles and formulations comprising type II microparticles mischaracterizes the data presented in the study and does not find basis in the study itself. The Declaration states that both type I and type II are small size particles. Moreover, the type I and type II formulations (both of which are encompassed by the instant claims as demonstrated by the discussion at page 2 of the Declaration) exhibit similar release profiles.

With respect to the Office allegations regarding the latent periods and the controlled release periods discussed in the Declaration, the Applicants respectfully submit that the Office has misinterpreted the data disclosed in the Declaration. The Applicants note that, in the WUTHRICH Declaration the delayed release time is calculated from the administration time to the peak time. The Applicants respectfully submit that one skilled in this art would recognize that the latent/delayed release may be calculated as the time to reach plateau, i.e. about 3 hours for perindoprilat release and about 1

hour for perindopril release. Thus, the data presented in the Declaration clearly demonstrate that the instant microparticle formulations provide a delayed and controlled release of perindopril, which release characteristics would not have been predicted based on the cited references of record in the instant application.

In view of the foregoing, the Applicants respectfully submit that the instant claims are not rendered obvious by the disclosure of the cited references. Reconsideration and withdrawal of the obviousness rejection under 35 USC § 103 is respectfully requested.

Finally, in accordance with MPEP § 821.04, the Applicants respectfully request rejoinder of withdrawn Claims 27, 29, and 31 upon the identification of allowable subject matter.

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Accordingly, entry of the present Response, rejoinder of withdrawn Claims 27, 29, and 31, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at the below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,



THE FIRM OF HUESCHEN AND SAGE

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Enclosure: Request for Continued Examination (RCE) under 37 CFR § 1.114;
Check No. 77727 (in the amount of \$810.00) for RCE Fee; Check No.
77726 (in the amount of \$1,110.00) for Three (3) Month Extension
Fee; and Postal Card Receipt.

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